



# Non-invasive Vagus Nerve Stimulation in Post-Traumatic Stress Disorder: A Clinical Practice Guideline from the Vagus Nerve Society

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## Abstract:

Post-traumatic stress disorder (PTSD) is a debilitating psychiatric condition stemming from exposure to traumatic events and is characterized by a spectrum of symptoms which impact daily life and mental well-being. Current treatment approaches, including psychotherapy and pharmacotherapy, often yield incomplete remission, necessitating the exploration of alternative interventions. Non-invasive vagus nerve stimulation (nVNS) presents a novel therapeutic option. nVNS can stimulate the vagus nerve at the auricular (ear) or the cervical (neck) level, modulating neural circuits implicated in PTSD without the invasiveness of traditional VNS. This paper briefly reviews the neurobiological basis of PTSD, explores the mechanisms of action of nVNS, and discusses safety and efficacy findings from recent clinical trials. The paper focuses on cervical nVNS (ctVNS) delivered by the gammaCore™ non-invasive vagus nerve stimulation (nVNS) device, as more published research is available for gammaCore nVNS. The Food and Drug Administration (FDA) granted Breakthrough Device Designation for PTSD for both auricular and cervical nVNS, but at this time, no direct comparisons of the two means of delivery in PTSD exist. Emerging evidence indicates that nVNS may effectively reduce PTSD symptoms by enhancing parasympathetic activity, attenuating sympathetic hyperactivity, and improving overall autonomic function. Further research is necessary to optimize treatment protocols and elucidate long-term benefits; however, we've provided some guidelines based on the existing literature and our experience. The designation of nVNS as a Breakthrough Device underscores its potential to address unmet needs in PTSD management, offering hope for improved outcomes and quality of life for affected individuals.

## 1. Introduction

Post-traumatic stress disorder (PTSD) is a prevalent and complex psychiatric condition that arises in response to exposure to traumatic events, significantly impacting an individual's quality of life. PTSD has a broad clinical presentation and is characterized by a diverse array of symptoms. The Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for PTSD involve experiencing a traumatic event, the presence of specific symptoms such as intrusive memories or nightmares, avoidance behaviors, negative changes in mood and cognition, and heightened arousal. PTSD can lead to chronic disability and an elevated risk of comorbid illnesses, including an increased susceptibility to other mental disorders such as substance abuse, depression, anxiety, and suicide<sup>1</sup>, as well as other medical conditions including fatigue, diabetes, autoimmunity, stroke, and myocardial infarction.<sup>2</sup> The level of disability stemming from PTSD alone can be comparable to severe depression or paraplegia and greater than blindness.<sup>3</sup>

PTSD afflicts military personnel and civilians alike. The national civilian 12-month and lifetime prevalence of PTSD are 4.7% and 6.1%, respectively, compared to the lifetime prevalence of 6.9% in Veterans.<sup>4,5</sup>

The neurobiology of PTSD includes alterations in brain structure and function. The amygdala, for example, which is responsible for processing emotions such as fear, can be hyperactive in individuals with PTSD, as has been well established in the literature.<sup>6</sup> Imbalances in neurotransmitters, such as increased levels of norepinephrine and decreased levels of serotonin, have been observed in published studies of symptomatic PTSD patients.<sup>7</sup> PTSD symptoms are associated with hypothalamic–pituitary–adrenal axis dysfunction as represented by imbalances in cortisol (such as higher cortisol levels<sup>8</sup> or low basal cortisol and an increased responsiveness to cortisol,<sup>9</sup> a dysregulated immune system, as well as an elevated pro-inflammatory state and metabolic dysfunction.<sup>10</sup> Cognitive processing and emotional responses, such as hyperarousal, also play a crucial role in the development and manifestation of PTSD.<sup>11,12</sup>

The mainstay of PTSD treatment has traditionally involved exposure therapy, pharmacotherapy, or a combination of the two. Psychological therapies also include trauma-focused cognitive behavioral therapy (CBT) and eye movement desensitization reprocessing (EMDR). CBT places an emphasis on helping individuals to develop coping skills whereby they can learn to modify their own thinking, problematic emotions, and behavior. During EMDR, the recall of a specific troublesome experience is triggered while a side-to-side visual stimulus is deployed by a therapist. These concomitant modalities are thought to help reduce emotive aspects via amygdala deactivation.<sup>13</sup>

Medications prescribed for PTSD modulate neurotransmitters (serotonin, norepinephrine, gamma-aminobutyric acid (GABA), the excitatory amino acid glutamate, and dopamine, among others), which can affect the fear and anxiety circuitry of the brain. However, no disease-modifying agents for PTSD are currently available for use in clinical practice. Also, only sertraline and paroxetine are approved by the Food and Drug Administration (FDA) for the treatment of PTSD. Many other medications are used off-label, and some, including benzodiazepines, can have a deleterious effect on PTSD symptoms in patients.<sup>14</sup>

Poor adherence, which is related to the stigma attached to psychopharmacological agents, their side-effect profiles, and poor feasibility in following psychotherapy sessions, contributes to poor treatment outcomes. As a result, despite advances in both forms of treatments and their strategies, only one-third of individuals with PTSD are able to achieve full remission with available standard therapies.<sup>15</sup>

Over the last two decades, a wealth of research has been conducted on PTSD. The amount of research is a huge advantage to the mental health community, which in the late 1990s had only 15 controlled trials regarding treatment for PTSD.<sup>16</sup> In the wake of technical advances in the field of neuroscience, newer forms of treatments have been developed and investigated.

Approved non-pharmacologic alternatives for the treatment of PTSD are extremely limited. Two recently FDA-cleared/approved devices include the NightWare Kit and the Freespira device. While both devices are indicated to alleviate PTSD symptoms through the reduction of sleep disturbance or breathing modification, respectively, they do not directly treat PTSD or its underlying pathophysiology. Stellate ganglion blocks have also recently received attention, designed to mitigate the sympathetic response in PTSD, but are invasive and require ongoing treatments. Additionally, less conventional therapies, such as the use of psilocybin mushrooms and LSD, have even been considered. Several other methods, such as slow and deep breathing, biofeedback, cold exposure, acupuncture, massage therapy, laughter, singing, chanting, humming, and yoga, have a long history of reported use but with minimal data or formal studies.

## 2. VNS

The vagus nerve serves as a unique bridge between the central functions of the brain and the peripheral organs. Originating in the brainstem, the vagus nerve contains sensory and motor fibers that influence peripheral organ function while also transmitting information about these organs back to the brain. Its efferent fibers primarily regulate the parasympathetic nervous system, providing

a counterbalance to the sympathetic nervous system. The afferent fibers relay sensory information from the visceral organs to the brain through the nucleus tractus solitarius in the medulla oblongata and the locus coeruleus in the pons. This information is then transmitted to brain areas involved in emotional regulation and stress response, including the amygdala and the anterior cingulate/ prefrontal cortex, which are known to be implicated in PTSD. Additionally, the efferent branches of the vagus nerve modulate inflammatory responses and autonomic tone by enhancing parasympathetic activity and reducing sympathetic activity, thereby increasing heart rate variability.<sup>17</sup>

The original form of vagus nerve stimulation (VNS) devices consists of an implantable, battery-powered VNS therapy pulse generator and a VNS therapy lead. There is also an external programming system that is used to change the stimulation setting according to the needs of the subject. The VNS therapy lead is placed surgically around the left vagus nerve in the carotid sheath and connected to a subcutaneous programmable pacemaker device that is placed over the left chest wall. Currently, an implantable VNS device is a Food and Drug Administration (FDA) approved treatment for chronic epilepsy, refractory epilepsy, and treatment-resistant depression.

Recent studies have expanded the application of implantable VNS to mental disorders beyond treatment-resistant major depression, including schizophrenia<sup>18</sup> and obsessive-compulsive disorder.<sup>19</sup> The effectiveness of VNS in these psychiatric conditions is likely due to its beneficial impact on the autonomic nervous system, particularly in stress-related responses.<sup>20</sup> VNS improves autonomic dysfunction by reducing sympathetic activity and enhancing parasympathetic tone.<sup>21</sup> Additionally, VNS modulates fear circuits<sup>22</sup>, induces neural plasticity<sup>23</sup>, enhances memory and cognition<sup>24,25</sup>, and boosts central neurotransmitter function<sup>26</sup>, including norepinephrine. VNS also has anti-inflammatory effects<sup>27,28,29,30</sup> as well as modulation of the default mode network of the brain. Active during resting moments, the default mode network (DMN) is a core, canonical brain network central to all other cerebral networks and is particularly important in alleviating depression.<sup>31</sup>

The requirement for surgical implantation, however, has limited the widespread implementation of VNS to psychiatry despite the fact that VNS can target the underlying neurobiological disturbances.

Non-invasive cervical vagus nerve stimulation (nVNS) is a relatively new approach, which also stimulates the vagus nerve, but without the cost and morbidity associated with an implantable VNS system. The neck is the ideal place to stimulate the vagus, as the majority of the fibers of the vagus nerve can be accessed there in a simple and non-invasive way.

gammaCore™ non-invasive vagus nerve stimulator (nVNS) is a small, handheld, user-administered therapy with 6 FDA-cleared indications for headache conditions. gammaCore nVNS is applied directly to the neck, just medial to the sternocleidomastoid muscle, where the vagus nerve travels along through the carotid sheath on its way to the brain. Computational modeling<sup>32</sup> and electrophysiological studies<sup>33</sup> have validated that gammaCore stimulates afferent fibers of the vagus nerve via access from the cervical region. Resting functional magnetic resonance imaging (fMRI) studies have demonstrated that gammaCore activates a dispersed neural network, including the primary target of the vagus nerve and the nucleus tractus solitarius (NTS), along with the insula, anterior cingulate, somatosensory cortex, thalamus, prefrontal cortex, medulla, hippocampus, and hypothalamus.<sup>34</sup>

Since the vagus nerve also reaches the skin at the outer acoustic canal and ear, and reflex responses such as the ear-cough-reflex or the auriculo-cardiac reflex have been observed upon auricular stimulation, the ear seems well suited for transcutaneous VNS. However, vagus nerve fibers are far less present in the auricular branch of the vagus (ABVN) nerve than the cervical vagus nerve<sup>35</sup>, as the ABVN has five to six times less the number of vagus fibers identified in the cervical region.<sup>36,37,38</sup> All of the auricular fibers are afferent and enter the trigeminal islands in the brainstem. This difference in afferent and efferent fibers, the number of fibers, and the location of the NTS and trigeminal may explain why some individuals do not experience therapeutic effects after treatment with auricular nVNS,<sup>39</sup> although some do not experience benefit from auricular nVNS as well.

### 3. Cervical nVNS in PTSD

#### Safety

Cervical non-invasive vagus nerve stimulation has been extensively studied in numerous sham-controlled trials, demonstrating an excellent safety profile. Studies report few minor adverse events, and those reported are temporary and infrequent. No serious device-related adverse events have been reported since the introduction to market. gammaCore has been approved for the European market since 2011 and in the US since 2017. gammaCore has been commercially available in the United States since 2018, with earlier iterations of the device available in 2017. Based on the historical use of the device, it has a well-established safety and tolerability profile.

By optimizing the parameters of the stimulation waveform, gammaCore targets the vagus nerve safely and directly. gammaCore produces a low-voltage electric signal consisting of five 5000-Hz pulses that are repeated at a rate of 25 Hz, which has been shown

to be well tolerated by patients with migraine and cluster headache. The waveform of the gammaCore pulse is approximately a sine wave with a peak voltage limited to 24 volts when placed on the skin, and a maximum output current of 60mA. Dramatically different physiological responses can be elicited with even the slightest changes to the electrical signal. As such, it is an important distinction to note that other devices do not use this same proprietary signal. Also, a key to the safety of the device is gammaCore's ability to stimulate only thick myelinated fibers without activating the reduced diameter unmyelinated C fibers. C fibers have higher stimulation thresholds and potential for cardiac side effects.

## Efficacy

Current research suggests that VNS effectively reduces PTSD symptoms. In both patients with PTSD and patients with a history of exposure to trauma, but not specifically diagnosed with PTSD, nVNS was shown to:

- Significantly reduce PTSD symptoms after three months<sup>40</sup>
  - Decreases in PTSD checklist scores ( $p < 0.05$ )
  - Decreases in HAM-A scores ( $p < 0.05$ )
  - Increases in IL-6 levels for the sham (but not the nVNS) group
  - CGI-I scores improvements ( $p = 0.003$ ) when sham-treated patients switched to nVNS
- Attenuate the neurobiological stress-response associated with PTSD<sup>41,42</sup>
  - Decreases sympathetic function
  - Lower HR ( $p < 0.01$ )
  - Greater PPG amplitude ( $p < 0.05$ )
  - Faster PAT ( $p < 0.0001$ )
  - Greater decreases in long-term HR variability ( $p < 0.05$ )
- Improve attention, declarative and working memory, which can improve the quality of life and productivity in patients with PTSD<sup>43</sup>
- Modulate autonomic tone/nervous system, improve recovery from traumatic stress, and enhance parasympathetic function<sup>44,45</sup>
- Significantly decrease peripheral and cardiac sympathetic activity and vascular measures in PTSD<sup>46</sup>
  - Increases in PPG amplitude during ( $p = 0.036$ ) and after ( $p = 0.044$ ) stimulation
  - Increases in PEP after stimulation ( $p = 0.035$ )
  - Greater increases in parasympathetic activity
  - Decreases in RR after stimulation ( $p = 0.002$ )
- Decrease neural reactivity to an emotional stressor<sup>47,48</sup>

Preclinical evidence for prevention/treatment of comorbid traumatic brain injury (TBI) and PTSD with nVNS showed that mice exposed to blast forces modeled on those encountered in combat demonstrated increases in stress-related maladaptive behaviors, which were ameliorated when nVNS was delivered 1 hour after blast exposure.<sup>49</sup>

Several additional studies are also underway. (ClinicalTrials.gov IDs: NCT05517304, NCT04437498)

## 4. gammaCore™

gammaCore was granted Breakthrough Device Designation for Post-Traumatic Stress Disorder (PTSD) by the US Food and Drug Administration in January 2022. gammaCore nVNS has not yet been approved by the FDA for use in PTSD.

The device is a multi-use, handheld, rechargeable, portable device consisting of a rechargeable battery and signal-generating and amplifying electronics, with a slide control switch for user/operator adjustment of the signal amplitude (relative range, 0-40 continuous). The gammaCore Sapphire:

- Includes a charging station incorporated into a storage case.
- Provides visible and audible feedback regarding the device and stimulation status.
- Allows for multiple stimulations or doses (each lasts 120 seconds, after which the device automatically turns off unless turned off earlier by the user/operator). Once the maximum daily number of doses has been reached, the device will not deliver any more

doses until the following 24-hour period.

- Can be programmed to deliver 24 doses per day for 31 or 93 days, or 12 or 36 months, based on the health care provider's prescription. Additional (refill/reload) cards can be provided (based upon a health care provider's prescription).

## 5. Patient Selection/Screening

Patient selection for treatment with gammaCore for PTSD involves careful consideration of several factors to ensure optimal outcomes. Candidates typically include individuals who have been diagnosed with PTSD and have not responded adequately to first-line therapies such as psychotherapy and medications. It is essential to assess the severity and chronicity of PTSD symptoms, and to continually reassess during treatment. Additionally, patient preference, likelihood to adhere to treatment, and willingness to use a non-invasive neuromodulation device should be considered. Those subjects with active implantable devices like a cardiac pacemaker should be excluded. Overall, a comprehensive evaluation by a health care provider experienced in treating PTSD is crucial to identify suitable candidates who may benefit from gammaCore therapy.

Contraindications for the use of nVNS are:

- An active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device
- Using another device at the same time (e.g., TENS Unit, muscle stimulator)

Informed consent is granted before the start of nVNS, and the potential subject given an explanation of all the possible side effects and their probability.

To apply the gammaCore device for PTSD, the patient should:

1. **Locate the Pulse:** Find the pulse on either side of the neck. This is where the vagus nerve is located.
2. **Prepare the Device:** Remove the cap and apply a pea-sized amount of the provided conductive gel to each stimulation surface.
3. **Apply the Device (may be applied to either side of the neck):** Turn on gammaCore and place it over the treatment location. Gradually increase the stimulation intensity until slight muscle contractions are noticed at the corner of the mouth. Most users find an intensity level between 15 and 25 effective.
4. **Treatment Frequency:** For PTSD and trauma-related conditions, apply two consecutive two-minute stimulations at the earliest sign of distress or anxiety. For ongoing management, apply two consecutive treatments three times a day. The first daily treatment should be applied within 1 hour of waking. The second daily treatment should be applied mid-day. The third daily treatment should be applied in the evening. A maximum of 24 doses (of two minutes each) could be used per day.
5. **Consistency and Adjustment:** Consistency is key. Use the device daily and adjust the placement slightly if muscle contractions are not felt.
6. **Cleaning and Maintenance:** After use, the stimulation surfaces should be cleaned with a recommended disinfectant and allowed to air dry.

Adequate patient training is necessary for success. For more detailed instructions and video demonstrations, refer to the gammaCore website.

gammaCore can be used adjunctively with existing medications.<sup>50</sup>

The critical outcome should be clinician-rated PTSD symptoms. Other important outcomes include self-reported PTSD symptoms and other clinical outcomes such as dropout and comorbid symptoms, quality of life, and safety.

## 6. Discussion/Conclusion

The consensus highlights that PTSD, with its multifaceted symptomatology and complex neurobiological underpinnings, often proves resistant to conventional psychotherapeutic and pharmacological interventions. Practicing clinicians don't have a consistent method to address the physiological changes of PTSD in patients. The gammaCore device, a non-invasive cervical vagus nerve stimulator, has been shown to safely, effectively, and efficiently target key neural circuits and biological pathways implicated in PTSD. This approach offers a novel mechanism for attenuating subjective reported PTSD symptoms, reducing sympathetic hyperactivity, and enhancing parasympathetic tone, thereby addressing both psychological and physiological aspects of the disorder. Its ability to activate the vagus nerve without the risks associated with surgical implantation of traditional VNS systems marks a significant advancement. There is an ongoing need for research and clinical trials to refine usage protocols and establish the long-term benefits of nVNS in treating PTSD. These efforts are crucial for improving patient outcomes and quality of life in this high-risk population.

## Indications and Important Safety Information

gammaCore™ (non-invasive vagus nerve stimulator) is intended to provide non-invasive vagus nerve stimulation (nVNS) on the side of the neck. gammaCore is indicated for:

- The preventive treatment of migraine headache in adolescent (age 12 and older) and adult patients.
  - The acute treatment of pain associated with migraine headache in adolescent (age 12 and older) and adult patients.
  - Adjunctive use for the preventive treatment of cluster headache in adult patients.
  - The acute treatment of pain associated with episodic cluster headache in adult patients.
  - Treatment of hemicrania continua and paroxysmal hemicrania in adults.
- The effectiveness of gammaCore has not been established in the acute treatment of chronic cluster headache
- gammaCore is contraindicated for patients if they:
- Have an active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device
  - Are using another device at the same time (e.g., TENS Unit, muscle stimulator) or any portable electronic device
- Safety and efficacy of gammaCore have not been evaluated in the following patients:
- Patients diagnosed with narrowing of the arteries (carotid atherosclerosis)
  - Patients with a metallic device, such as a stent, bone plate, or bone screw, implanted at or near the neck
  - Patients who have had surgery to cut the vagus nerve in the neck (cervical vagotomy)
  - Pediatric patients (younger than 12 years)
  - Pregnant women
  - Patients with clinically significant hypertension, hypotension, bradycardia, or tachycardia

NOTE: This list is not all inclusive. Please refer to the gammaCore Instructions for Use for all of the important warnings and precautions before using or prescribing this product.

Available by prescription only. US Federal Law restricts this device to sale by or on the order of a licensed health care provider.

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